Remarks

Before addressing specifically the rejections repeated by the Examiner, Applicant believes that it would be fruitful to address Examiner's response to Applicant's previous arguments.

It may be helpful to outline the essentials of the presently claimed invention. The instant invention relates to the detection of target proteins in a sample. A first RNA, putatively specific for the protein target, interacts and binds to the target protein. When the first RNA binds to the target protein, the *cis* regulatory element of the first RNA (the "C" sequence) is rendered inoperable thereby allowing for the first RNA to serve as a template for RNA synthesis. A second RNA is synthesized, using the first RNA as a template, such that it is complementary to the first RNA. However, should the first RNA NOT interact with and bind to a target protein, then the "C" *cis* regulatory element will prevent synthesis and thus the formation of the second RNA molecule.

The Examiner first argues that it is improper for Applicants to attack the individual references cited against the invention where the rejections are based on combinations of references.

"It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements." Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 43 USPQ 2d 1294 (Fed. Cir. 1997). Examiner is arguing that separate elements of the presently claimed invention are recited in the various references cited. Then, argues the Examiner, there is some motivation to combine these elements to arrive at Applicants' claimed invention. As a predicate to this argument process, the references themselves must disclose at least one element of the presently claimed invention. Therefore, it is perfectly legitimate to demonstrate that the references do not even recite one or more of the elements claimed in the present invention. If the recited references lack one or more

of the elements of claimed invention, then a *prima facie* case of obviousness cannot be established - to think otherwise is clearly counterintuitive. Hence, Applicants' arguments refuting the cited references with respect to whether they recite one or more of the elements of the claimed invention is completely proper.

Next, the Examiner lists several limitations in which, he claims, are not recited in any of the claims. To assist the Examiner, we will indicate the limitations using claim 1: key - italicized language is the actual claim language that is present and reflects what the Examiner claims is <u>not</u> recited, the Examiner's assertion from the 10-17-03 Office Action is bracketed [xx] after the applicable italicized claim language.

1. A composition for determining the presence or absence of a *target molecule comprising a first ribonucleic acid (RNA) molecule*[(d) the ligand is an RNA molecule], said first RNA molecule binds a target molecule and has the following formula:

5'-A-B-C-D-E-3';

wherein A is a section of the RNA molecule having 10-100,000 nucleotides which section is, with another RNA sequence, E, replicated by an RNA replicase, *the letter "B" denotes a section of the RNA molecule having approximately 1 to 50000 nucleotides which section, with another sequence D, binds the target molecule under binding conditions, wherein said target is a small or large organic molecule selected from the group consisting of a peptide, protein, and derivatives thereof*[(b) a target protein molecule has to bind with sections "B" and "D" ...], the *letter "C" denotes a section of the RNA molecule having approximately 1 to 10000 nucleotides which section is capable preventing the replication of the first molecule by the RNA replicase*[(a) section "C" comprises stop sequence], the letter "D" denotes a section of the RNA molecule having approximately 1 to 50000 nucleotides which section, with another sequence B, binds the target molecule under binding conditions, the sections B and D, in combination, comprise in total at least 10 nucleotides, the first RNA molecule, *with sections B and D bound to target, is acted upon by the RNA replicase to form a second RNA molecule, said second RNA molecule has the following formula*[(e) if target protein is present ... synthesis of second RNA molecule]:

5'-E'-X-A'-3';

wherein, E' is the complement to E, and A' is the complement to A, and the letter "X" denotes the complement of parts of the sections B and D which may be replicated, or the letter denotes the direct bond between sections E' and A', and said second RNA molecule is replicated by the RNA replicase under replicating conditions.

As can be seen from above, every limitation (bracketed language) that the Examiner contends is absent from the recited claim is in fact present (italicized language). Therefore, the limitations are in fact recited in the claims.

Next, in response to Applicants' argument that there is a paucity of motivation to combine the references cited, the Examiner asserts that Holy provides "strong motivation" to combine references. As stated below, the Holy reference is significantly different from the presently claimed invention. Holy is directed to the use of antibodies in the detection of a target molecule. The antibody is labeled thus facilitating the detection of a complex, *i.e.*, the antibody-target complex. The Examiner states, quoting from Holy, "In one embodiment of this alternative, antibodies are raised against the compounds of this invention. Such antibodies bind to the analogue of this invention and thereby are useful in detecting its presence as label for a protein or oligonucleotide" The Examiner concludes by stating, "Similar logic is applicable to other combinatory references."

Applicants reiterate, the claimed invention concerns the use of nucleotides and not antibodies for binding a target. If the Examiner is equating a nucleic acid with an antibody, then Applicants can only suggest that one skilled in the art can clearly distinguish between the two macromolecules and understand the inherent technological differences that exists between technologies employing the two. In the case at hand, an antibody is not an analogous molecule. For example, it can not serve as a template for a replicase as is true for the claimed invention's RNA molecule. To employ the Examiner's final comment, *i.e.*, similar logic ..., one could say, given Holy, that any further development in detection of targets is anticipated based on Holy - this simply is not the case. One using antibodies to detect the presence of a target molecule in a sample would not be motivated to try using nucleic acids. These are two separate technologies which need not be explained. How's does one go from using a labeled antibody to using a first nucleic acid for binding and a second nucleic acid for signaling? The mechanisms (for example, signaling) involved in the technologies are completely diverse.

Applicants assert that Holy is an inappropriate reference and should never have been employed.

Next, the Examiner discusses Applicants' arguments concerning the issue of reasonable expectation of success. The Examiner quotes from the MPEP and cases regarding this issue which actually does not address Applicants' arguments. Applicants fail to understand how the Examiner can insist that based on the reference cited one skilled in the art would have a reasonable expectation of success in arriving at the claimed invention. For example, one skilled in the art reading Holy and the use of antibodies for detecting a target in a sample could not arrive at the presently claimed invention using a complex nucleic acid. If the Examiner could explain how one skilled in the art after reading Holy would arrive at the presently claimed invention, this would be of benefit to Applicants. This is true of any one or combination of references cited. One reason why these references fail is that either alone or in combination they fail to disclose the claimed invention - then how are they going to arrive at the claimed invention? In order for there to be any reasonable chance of success, the prior art would have to be modified, as the Examiner states in the present Office Action. Applicants assert that such modifications would include drastic modifications. The Examiner states that the Holy reference is "an invitation to research." This is the argument for showing a reasonable expectation of success. Applicants agree that Holy may serve to invite others to conduct research, but the possibility that such research would arrive at Applicants' invitation is highly suspect.

The following are formal arguments directed towards the repeated arguments proffered by the Examiner.

Claims 1-8, 11 and 12 are rejected under 35 USC § 112, second paragraph

Claims 1-8, 11 and 12 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The amendments presented above should alleviate the concern of the Examiner. The Examiner specifically alludes to the use of the phrase "such as" in the claims. This phrase has been deleted in the amended claims. Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 1-8 are rejected under 35 USC § 103(a)

Claims 1-8 are rejected under 35 USC § 103(a) over Marsh *et al.* in view of Spiegelmen further in view of Holy *et al.* (US Pat. No. 5,977,061). Applicants respectfully disagree.

The Examiner posits that Marsh *et al.* teach a method of determining the presence or absence of a target molecule. Further, that Marsh *et al.* [*sic*] "does not teach a composition by providing paired RNA molecules. Marsh *et al.* does not teach section "C" of the RNA molecule which section is capable of preventing the replication of the first molecule by the RNA replicase." *Office Action* dated 8/14/03, pg. 5.

The Examiner further characterizes Spiegelman as teaching [*sic*] "a customized preparation of RNA templates ... Spiegelman teaches section "C" of the RNA molecule which section is capable preventing the replication of the first molecule by the RNA replicase." *Office Action* dated 8/14/03, pp. 5-6.

The Examiner states that [*sic*] "Holy *et al.* teaches the nucleic acid, wherein the target is a small or large organic molecule such as a peptide, protein, and derivatives thereof, which can be attached to the analogues of known bases or nucleotides." *Office Action* dated 8/14/03, pg. 7.

In order to establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim

limitations." M.P.E.P. §2143, see also, *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

A case of *prima facie* obviousness is not been established. The presently claimed invention claims a composition for determining the presence or absence of a target molecule comprising a first RNA molecule that binds the target molecule of interest. The first RNA molecule has the formula of:

5'-A-B-C-D-E-3'

wherein A is a section of the RNA molecule together with section E is replicated by a replicase; "B" denotes a section of RNA sequence together with "D" that actually binds the target molecule under proper binding conditions; "C" is a section of RNA that is capable of preventing replication. Once the target molecule is bound by sections "B" and "D" a replicase acts upon the complex to form a second RNA molecule having the following formula:

5'-E'-X-A'-3'

wherein, E' is the complement to E, and A' is the complement to A, and "X" denotes the complement of parts of "B" and "D" that can be replicated, or the direct bond between sections E' and A'.

Applicants claim a composition comprising paired RNA molecules having a first RNA molecule and a second RNA molecule. The first RNA molecule binds a target molecule and has the following formula:

5'-A-F-B-3'

and a second RNA molecule that binds a target molecule having the following formula:

5'D-H-E-3'

wherein, A and E are subject to replication by a replicase, "B" and "D" denote sections responsible for binding to a target molecule, "F" forms a hybridization product with section "H" that allows for replication of sections A and E to form a third RNA molecule having the formula:

5'-E'-X-A'-3'

wherein E' is the complement to E and A' is the complement to A, "X" denotes the complement of parts of "F" and "H" that can be replicated, alternatively, "X" denotes the direct bond between E' and A' and this third RNA molecule is subject to replication.

As stated above, a requirement to establish a *prima facie* case of obviousness requires that the prior art reference (or references) must teach or suggest all of the claim limitations - this requirement is simply not met by Marsh either alone or in combination with Spiegelman and/or Holy.

As stated above, Marsh fails to recite an RNA molecule having the formula 5'-A-B-C-D-E-3' nor does Marsh disclose an RNA having the formula 5'-A-F-B-3' nor 5'-D-H-E-3' with the attendant limitations of these formulae. For example, there is no analog to RNA sections "B" and "D" as claimed by Applicants in the Marsh disclosure. Recall, these sections in Applicants' invention form secondary structure and are employed to bind a target molecule, specifically a protein target. Marsh fails to recite any analogous RNA regions. Still another example, "F" and "H" which serve to form a hybridization product in Applicants' claimed invention is completely absent in Marsh. Further, unlike the presently claimed invention, Marsh fails to disclose a paired RNA molecule composition.

Moreover, section "C" as claimed by Applicants is completely absent from Marsh, as adroitly pointed out by the Examiner on page 5 of the *Office Action* dated 8/14/03. In the presently claimed invention, section "C" is a stretch of RNA that can be used to inhibit replicase activity. The Examiner points out that Marsh has an analogous section that serves as a non-base-paired spacer to facilitate access of the replicase to the promoter. This simply is not equivalent to that which is presently claimed. Applicants in the specification characterizes section "C" as comprising "stop" sequences. This is very different than just a spacer element. Therefore, Marsh fails to recite an equivalent to sequence "C" of Applicants' presently claimed invention.

Further, in order to arrive at the claimed second RNA molecule, a target (protein) molecule has to bind with sections "B" and "D" of the first molecule, then replicase activity takes place. There is no analogous disclosure to be found in Marsh *et al.*

Spiegelman fails to rectify the deficiencies of Marsh. Spiegelman fails to recite an RNA molecule having the formula 5'-A-B-C-D-E-3' nor does Speigelman disclose an RNA having the formula 5'-A-F-B-3' nor 5'-D-H-E-3' with the attendant limitations of these formulae. For example, there is no analog to RNA sections "B" and "D" as claimed by Applicants in the Spiegelman disclosure. Recall, these sections in Applicants' invention form secondary structure and are employed to bind a target molecule, specifically a protein target. Spiegelman fails to recite any analogous RNA regions. Still another example, "F" and "H" which serve to form a hybridization product in Applicants' claimed invention is completely absent in Spiegelman. Further, unlike the presently claimed invention, Spiegelman fails to disclose a composition by providing a paired RNA molecule.

Moreover, section "C" as claimed by Applicants is completely absent from Spiegelman. In the presently claimed invention, section "C" is a stretch of RNA that is contiguous with the other sections of the RNA molecule and can be used to inhibit replicase activity. The Examiner suggests that Spiegelman has an analogous section. The "interfering compound" as Spiegelman puts it is an RNA molecule independent from the viral RNA molecule of interest. The interfering compound comprises nucleotide sequences that will interact with a replicase thus precluding replication of the independent viral RNA. This simply is not equivalent to Applicants' claimed invention. Section "C" in the presently claimed invention comprises "stop" sequences that is contiguous with the larger RNA molecule.

Further, in order to arrive at the claimed second RNA molecule, a target (protein) molecule has to bind with sections "B" and "D" of the first molecule, then replicase activity takes place. There is no analogous disclosure to be found in Spiegelman.

Holy *et al.* disclose nucleotides that can be used as intermediates in the formation of flame retardants, diagnostic reagents and therapeutics, including antivirals. See Abstract of '061. One embodiment of the '061 patent involves producing antibodies against a nucleotide of the invention. These antibodies can be labeled and be used to bind with analogues of the invention, thereby detecting it. See, '061, columns 12-13, lines 64 -2.

Holy is significantly different from the presently claimed invention. The target class of molecules in Holy are nucleotides as well as other proteins and the ligand is a protein, the produced antibodies. Whereas, in the presently claimed invention, the target molecules are proteins and the ligand is an RNA molecule.

Moreover, the detection mechanisms are quite different. In Holy, the antibody produced against a particular nucleotide is labeled and if, and when, it interacts with its target the complex can be detected. In the presently claimed invention a first RNA molecule must first bind to a target molecule, then and only then, is said first RNA molecule replicated forming a second RNA molecule. This replication of the first RNA forming the second RNA can serve as a signal for detecting the presence of the target in a given sample. The second RNA molecule can go on to be further replicated. A reiterative cycle can be envisaged, the reagents and replicase activity are obviously limiting.

The scenario disclosed in Holy is quite different what is claimed in the present invention. To reiterate, a first RNA molecule is used to interact with a target molecule, a protein, in a complex sample. If the target protein is present, then the first RNA will interact and bind thereto. Once bound, the first RNA molecule can serve as a template for the synthesis of a second RNA molecule. The production of the second RNA molecule can then serve as a signal amplification event. If, however, the target protein is absent from the sample, then, the first RNA will <u>NOT</u> serve as a template for RNA synthesis. In Holy, the antibody serves as the ligand, whereas in the presently claimed invention it is the first RNA molecule that serves as the ligand. (Here ligand is

understood to mean that molecule that interacts with a target molecule.) Clearly, Holy is significantly different from the presently claimed invention. Applicants respectfully request reconsideration and withdrawal of the present reject.

Claims 11 and 12 are rejected under 35 USC § 103(a)

Claims 11 and 12 are rejected under 35 USC § 103(a) over Marsh *et al.* in view of Spiegelmen further in view of Holy *et al.* (US Pat. No. 5,977,061) further in view of the Stratagene Catalog. Applicants respectfully disagree.

The deficiencies of Marsh and Spiegelmen have been presented above and need not be repeated here. The arguments presented above apply equally here as well.

As stated previously, Holy *et al.* disclose nucleotides that can be used as intermediates in the formation of flame retardants, diagnostic reagents and therapeutics, including antivirals. See Abstract of '061. One embodiment of the '061 patent involves producing antibodies against a nucleotide of the invention. These antibodies can be labeled and be used to bind with analogues of the invention, thereby detecting it. See, '061, columns 12-13, lines 64 -2.

As described above, Holy is significantly different from the presently claimed invention. The target class of molecules in Holy are proteins as well as nucleotides and the ligand is a protein, the produced antibodies. In the present invention, the target class of molecules include protein molecules and the ligand is a nucleotide molecule. (See previous discussion for detail arguments against Holy.)

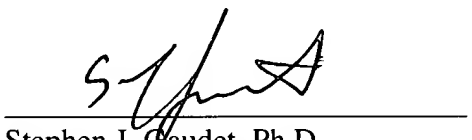
The Stratagene Catalog fails to rectify the deficiencies found in the cited references. The Stratagene Catalog does disclose various kits having various reagents, however, this is wholly insufficient to establish a case of *prima facie* obviousness. In order for Stratagene to be effective in establishing a case of obviousness, it would have to rectify the deficiencies found in the other cited references. Moreover, there would have

to be a suggestion or motivation for one to combine Stratagene with any of the other cited references. This suggestion or motivation is completely lacking in either reference.

Marsh *et al.* either alone or in combination with Spiegelman and/or Holy does not establish a *prima facie* case of obviousness. Moreover, there is a paucity of motivation to combine these references and even if one did, there is no reasonable expectation of success that by such combination one would arrive at the presently claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner is invited to call the undersigned attorney at (617) 854-4237 should he determine that a telephonic interview would expedite prosecution of this case.

Respectfully submitted,



Stephen J. Gaudet, Ph.D.
Attorney for Applicants
Reg. No. 48,921

Date: 11/20/03